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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/726,904
Filing Date: December 02, 2003
Appellant(s): AOKI ET AL.

Stephen Donovan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 2, 2008 appealing from the Office action mailed April 07, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

10/461,829

10/460,898

10/933,723

10/443,593

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

2001/0018415	Aoki et al.	8-2001
6,113,915	Aoki et al.	9-2000
2003/0118598	Hunt	06-2003

Kohl A., et al., 'COMPARISON OF THE EFFECT OF BOTULINUM TOXIN A (BOTOX) WITH THE HIGHLY-PURIFIED NEUROTOXIN (NT201) IN THE EXTENSOR DIGITORUM BREVIS MUSCLE TEST." Movement Disorders, 2000, No. 15, Supp. 3, page 165.

Schantz, E., et al., 'PROPERTIES AND USE OF BOTULINUM TOXIN AND OTHER MICROBIAL NEUROTOXINS IN MEDICINE,' Microbiological Reviews, March 1992, pp. 80-99.

Tse et al., 'PREPERATION AND CHARACTERISATION OF HOMOGENOUS NEUROTOXIN TYPE A FROM CLOSTRIDIUM BOTULINUM' Eur. J. Biochem. Vol. 122, No. 3 (1982), pages 493-500

Han et al. 'EFFECT OF BOTULINUM TOXIN A CHEMODERNERVATION IN SENSORY STRABISMUS." Journal of Pediatric Ophthalmology and Stabismus, Vol. 38, No. 2 (2001) pp. 68-71.

Balkan et al. 'A FIVE YEAR ANALYSIS OF BOTULINUM TOXIN TYPE A INJECTIONS: SOME UNUSUAL FEATURES.' Annals of Opt homology, vol. 23, No. 9 (Sep. 1991), pp. 326-333.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The MPEP states:

> The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the prior application and in the later-filed application must be **sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112.** See Transco Prods., Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The prior-filed application must disclose the common named inventor's invention claimed in the later-filed application in the manner provided by the first paragraph of 35 U.S.C. 112. See 37 CFR 1.78(a)(1). Accordingly, the disclosure of the prior-filed application must provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph."

See MPEP 201.11. Thus, the parent application must comply with both written description and enablement under 35 U.S.C. 112 First Paragraph.

In the instant application the claims have been limited to the use of neurotoxic component of botulinum toxin, where the neurotoxic component is 150 kilodaltons. The Parent application limited the disclosure of botulinum toxin to botulinum toxin complex, where the molecular weight was greater than 150 kilodaltons. The parent applications 08/627,118 and 08/173,996 did not provide sufficient enabling disclosure for using the 150 kilodalton neurotoxic component only in the treatment of stabismus.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or

absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention

The invention is drawn to use of botulinum toxin for treating stabismus.

(2) The state of the prior art

In response to an obviousness rejection Appellants stated on the response dated September 26, 2006 that there was a "General Belief That Pure Botulinum Toxin is Clinically Ineffective." Appellants asserted:

> "**[A]t the time of the filing of the present application, one of ordinary skill would not consider the teachings of Tse reference regarding use of purified botulinum toxin to be relevant to clinical treatment, such as the treatment of strabismus in humans**. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings, Specifically, Schantz et al. states:
>
> > Most recent information concerning the structure and pharmacology of botulinum toxin has been obtained with purified neurotoxins, but it is unlikely that these will be used in clinical settings. The toxin complexes are much more stable than neurotoxin and can be diluted and formulated with retention of toxicity. Pure neurotoxins can be kept for several weeks to months in solution in the cold but are inactivated on dilution, formulation, and drying.
>
> Schantz et al., Microbiological Reviews, Mar 1992, p. 80-99, 89, second column, emphasis added, Exhibit 2. Since it was believed at the time of filing the present application that pure botulinum toxin would not be effective for clinical use, one of ordinary skill would not be impelled to combine the teachings of the Tse reference (use of pure botulinum toxin in non-clinical settings, i.e., rat experiments) with the teachings of the Balkan/Han references (use of complexed botulinum toxin in clinical setting for treating stabismus in humans).
>
> It is important to note that Schantz et al. makes the statement quoted above even though Schantz ct al. was fully aware that pure botulinum toxin had been tested in rats. For example, the Schantz reference cited the Tse reference on the second

> column on page 83, and Sellin et al. (Acut Physiol Scan, 983; 119:127-33, hereinafter "the Sellin reference", Exhibit 3) on page 89, which reported on experiments similar to that of the Tse reference, i.e., injection of pure botulinum toxin type B into the lower hind limb of a rat to produce paralysis. Nevertheless, the Schantz reference asserted that the use of pure botulinum toxin would be clinically ineffective on page 89."
>
> "Also, note that Schantz et al. was published much later (1992) than Tse (1982). Moreover, Schantz was published in the year that was much closer in time to the priority filing date (1993) of the claimed invention. **Accordingly, the disclosure of Schantz et al. is more current than Tse, and is more reflective of the state of the art for when the present application was filed.**"

(3) The relative skill of those in the art;

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art;

Given Appellants summation of the art as of 1992, it is highly unpredictable to determine if the neurotoxic component could be used in a clinical setting.

(5) The breadth of the claims;

The claims are drawn to a method for treating stabismus, the method comprising the step of administering to a patient a therapeutically effective amount of a single or dichain form of the neurotoxic component of botulinum toxin to thereby treat the patient's stabismus, where the neurotoxic component administered to the patient has a molecular weight of about 150 kilodaltons.

(6) The amount of direction or guidance presented; (7) the presence or absence of working examples;

It is taught "Botulinum toxin is obtained commercially by establishing and growing cultures of C. botulinum in a fermenter and then harvesting and **purifying** the fermented mixture in accordance with known techniques. Botulinum toxin type A, the toxin type generally utilized in treating neuromuscular conditions, is currently available commercially from several sources; for example, from Porton Products Ltd. UK, under the trade name "DYSPORT," and from Allergan, Inc., Irvine, Calif., under the trade name BOTOX.®." (see page 4 of parent application 08/173,996 and 08/627,118). The examples in the specification utilize DYSPORT and BOTOX. BOTOX and DYSPORT are both commercially available toxin that are purified and contain the neurotoxic component as a complex see pages 8-9 and examples) . The specification is void of any examples that would establish the effectiveness of the neurotoxic component. While the specification talks about the different components of the botulinum toxin, the specification does not clearly indicated that one can use the purified component.

Appellants have stated "it was believed at the time of filing the present application that pure botulinum toxin would not be effective for clinical use." For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. . ." Appellants' parent Application was filed one year and eight months after the publication of Schantz reference. However, Appellants' specification neither disclosed nor implied that pure toxin was clinically ineffective, as recited by the state of the prior art at the time. The specification did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective. Given the state of the art as recited by Schantz, such information was **necessary and critical** to allow one of ordinary skill in the art to use pure toxin in a clinical setting in the treatment of patients. Without such guidance, one would be burdened with undue experimentation to practice the claimed invention. For the dosage, Appellants

have stated that determining the effective amount for a pharmaceutical agent (which would be the pure botulinum toxin in the present case) in a particular medical condition (which would be stabismus in the present case) is well within the ordinary skill in the art. However, given the teaching of Schantz, it is unclear how one would go about determining the effective amount. The parent application does not provide any guidance in this manner.

(8) The quantity of experimentation necessary.

Given the state of the art as recited by Schantz, such information was **necessary and critical** to allow one of ordinary skill in the art to use pure toxin in a clinical setting. Without such guidance, one would be burdened with undue experimentation to practice the claimed invention. Thus, since the parent application does not provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph, the priority under 35 USC §119 is denied for 08/173,996.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-5, 29, 47, 63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Kohl et al. and Tse et al. and Aoki et al. (US 6,113,915).

The claims are drawn to a method of treating stabismus using botulinum toxin.

Balkan et al. teaches the administration of botulinum toxin type A and type F for the treatment of strabismus (see abstract). The reference discloses that 37% of the patients treated with the toxin were cured and many showed significant improvement.

Han et al. describes the use of botulinum toxin type A in the treatment of strabismus (see abstract). The reference discloses a dosage of 1.24-5 units to a patient suffering from strabismus (abstract). Note that about 1.25-5 units is inclusive of the claimed range of claim 6. Furthermore, the reference discloses the same dosage range, alleviation of strabismus would necessarily be achieved. The difference between the Han et al. or Balkan et al and the instant application is that the reference does not teach the use of botulinum toxin having a molecular weight of 150kda.

However, Tse et al. teach that purified neurotoxin with a molecular weight of 1.4kda and removing the Haemagglutinin complex by affinity chromatography (see page 494). The reference states that neurotoxin free of Haemagglutinin, when injected into the hind leg muscle of a rat, produced local paralysis within 24 hours (see page 494). Further, as with impure neurotoxin, pure neurotoxin (mw 140 kda) specifically and characteristically inhibited stimulated and spontaneous release of acetylcholine at the vertebrate neuromuscular junction (see page 499). It should be noted that it is well known in the art that botulinum toxin complexes inhibit the release of acetylcholine resulting in local paralysis of the muscle (see page 1-2 of the instant specification). Aoki et al.

teaches that botulinum toxin complexes (MW greater than 150 kda) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection of botulinum toxin complex (see col. 5, lines 50-25).

Kohl et al. teaches the administration of botulinum toxin NT-201, a highly purified botulinum toxin that consists of pure neurotoxin. The results showed that that the paralytic effect of the pure neurotoxin appears to be faster with NT-201 based on 20% CMAP decline. The maximum effect of this toxin was comparable to the complexed neurotoxin (see page 165). Note that the subjects used were human male volunteers. Thus the effects observed in mouse model of Tse et al. were reflective in Kohl et al. Note that this reference was cited in Hunt (US2003/0118598), which has the same Assignment as the instant application, as the basis to conclude that pure botulinum toxin can be formulated into pharmaceutical formulations for human use. "[P]ure botulinum toxin has been used in humans. see e.g. Kohl A., et al., Comparison of the effect of botulinum toxin A Botox (R)) with the highly-purified neurotoxin (NT201) in the extensor digitorum brevis muscle test, *Mov Disord* 2000;15(Suppl 3):165. Hence, a pharmaceutical composition can be prepared using a pure botulinum toxin." (see page 4, paragraph 043).

Therefore, it would have been obvious to one of ordinary skill it the art to use pure neurotoxin for the treatment of strabismus because pure neurotoxin has similar activity in the paralysis of muscles as complexed neurotoxin and has similar activity against spontaneous release of actetylcholine and because that botulinum toxin complexes (MW greater than 150 kda) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection. There would be a reasonable expectation of success because Kohl et al. demonstrates a faster paralytic effect with purified botulinum toxin component in humans.

Claims 1-2, 4-5, 29, 47 and 63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Khol et al. and Aoki et al. (US 6,113,915) and Aoki et al. (20010018415).

The claims are drawn to a method of treating stabismus using botulinum toxin.

Balkan et al. teaches the administration of botulinum toxin type A and type F for the treatment of strabismus (see abstract). The reference discloses that 37% of the patients treated with the toxin were cured and many showed significant improvement.

Han et al. describes the use of botulinum toxin type A in the treatment of strabismus (see abstract). The reference disclose a dosage of 1.24-5 units to a patient suffering from strabismus (abstract). Note that about 1.25-5 units is inclusive of the claimed range of claim 6. Furthermore, the reference discloses the same dosage range, alleviation of strabismus would necessarily be achieved. The difference between the Han et al. or Balkan et al and the instant application is that the reference does not teach the use of botulinum toxin having a molecular weight of 150kda.

Aoki et al. (US 6,113,915) teaches that botulinum toxin complexes (MW greater than 150 kda) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection of botulinum toxin complex (see col. 5, lines 50-25). Aoki et al. (US 20010018415) teach The neurotoxic component of Botulinum toxin has a molecular weight of about 150 kilodaltons and is thought to comprise a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin, i.e., by interfering with the exocytosis of acetylcholine, by decreasing the frequency of acetylcholine release, and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to bind to the presynaptic membrane (see col. 1, paragraph 0007).

Therefore, it would have been obvious to one of ordinary skill it the art to use pure neurotoxin for the treatment of strabismus because botulinum toxin complexes (MW greater than 150 kda) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection and the 150 kda portion of the toxin has a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin, i.e., by interfering with the exocytosis of acetylcholine, by decreasing the frequency of acetylcholine release, and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to bind to the presynaptic membrane.

(10) Response to Argument

Arguments Regarding Denial of Priority under 35 USC §119

Appellants argue that the evidence as a whole demonstrates that the parent applications clearly enable one of ordinary skill in the art to use the neurotoxic component in a clinical setting. Appellants go through the Wands factors and argue that the art recognized how to purify and formulate neurotoxic component of botulinum toxin. Appellants argue that the parent applications disclose "different components of a botulinum toxin and clearly indicates that one can use both the single and dichain forms of the neurotoxic component." The parent application describes how to administer the neurotoxic component to a patient. "One of ordinary skill in the art would be skilled in determining proper dosage based on particular circumstances of a patient as well as being skilled in injections involving the eye in treatment of stabismus."

Appellants state that denial of priority has utilized a "strict standard that is improper under law." Appellants stress that it is not the art that must enable the claimed invention but the specification in light of the knowledge of one of ordinary skill in the art. By contending that the art

must enable the claimed invention, a stricter standard has been used and Appellant requests the Board to reverse the rejection for lack of enablement.

Appellants further contend, that even where the proper standard has been utilized, "the Examiner has essentially limited the evidence to be considered to a single publication, a review by Schantz et al." Appellants argue that the art, specifically referring to Lamanna C. et al, teach formulation and storage of the neurotoxic component of botulinum toxin. The parent application, according to Appellant, "describes many examples of administration of a botulinum toxin, a generic term used throughout the specification to embrace the family of botulinum toxins, including the neurotoxic component," specifically referring to Examples 2-2(e) for support.

Appellants state that the declaration by Dr. Brin and Dr. Smith provide evidence upon which the Declarants base their conclusions. Appellants state that the Declaration by Dr. Smith "refers to contemporaneous publication, such as a Ph.D. thesis. . .published March 10, 1994 . .and a review article by DasGupta." The Goodnough thesis describes a formulation of the neurotoxic component suitable for medical use using the same lyophilization process used for preparing botulinum toxin complex and DasGupta rebuts Schantz's opinion of the stability of neurotoxic component. The dismissal of the reference by the Examiner ignores the law "which clearly indicates that post-filing date publication are relevant if they provide evidence of the level of skill in the art at the time the application was filed."

Appellants assert that that the statements made in the responses dated September 26, 2006 were made in response to an obviousness rejection, "that one of ordinary skill in the art would not consider the Tse reference to be relevant to clinical treatment." The Examiner has confused the standards for enablement with the standards for obviousness. "Schantz is merely one publication to be considered among many other in the context of an objective enablement inquiry into the

evidence as a whole." Appellants make reference to Singh v. Brake, 317 F.3d 1334, 1345 (Fed.Cir. 2003) to support the difference between obviousness and enablement arguing that "[a]lthough the questions (1) whether or not a reference "teaches away" from a claimed invention and (2) whether or not a claimed invention provides "unexpected results" are relevant in determining whether or not a claimed invention would have been obvious, they are not the primary questions bearing on enablement."

Response to Arguments Regarding Priority

Appellants arguments fail to establish that the parent application 08/173996 and continuing application 08/627118 provide an enabling disclosure.

The MPEP states that, "[w]hether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains." See MPEP § 2164.05(a).

Appellants argue that a stricter standard has been utilized in determining that the parent Application disclosure is non-enabling. However, in determining a non-enabling disclosure of the parent applications, the nature of the invention, the state of the prior art, and the level of skill in the art were all considered. Indeed, in the response dated December 20, 2007 Appellants acknowledged that the non-enablement was premised on "on the fact that the specification [parent] did not provide

ample guidance on 'how to use' the neurotoxic component in a clinical setting. . . Applicants did not provide any guidance to one of ordinary skill in the art how one could avoid the problems associated with purified botulinum toxin component. . .as indicated by Schantz et al. the teachings of complexed toxin could not be utilized [for] purified botulinum toxin since the purified portion is so labile that it would not be used in clinical settings." Thus, the record clearly indicates that the denial of priority was not premised solely on whether the art, as of filing date of '996, provided ample guidance on how use the neurotoxic component in a clinical setting, but whether the record as a whole include disclosure in the parent application and the state of the art provide guidance on how to use the claimed invention.

Appellants have argued that the "specification need not provide 'ample guidance' on how to use a pure toxin in a clinical setting." However, the MPEP states "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling." See MPEP 2164.03. Here, it was Appellants who argued that that there was a general belief that that pure toxin was clinically ineffective, as of the filing date of the claimed invention. It was Appellants who argued that Schantz, "reflective of the state of the art for when the present application was filed," would lead one to conclude that "purified botulinum toxin is so labile that it would not be used in clinical settings." In essence "one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains" and thus one would conclude "there is lack of predictability in the art." See MPEP 2164.03. Thus, based on Appellants' statements, one of ordinary skill in the art would view using pure botulinum toxin in a clinical as unpredictable. Accordingly, unlike Appellants' contentions, the disclosure of the parent Applications 08/173,996

and 08/627,118 did need to provide "more detail as to how to make and use the invention in order to be enabling."

Appellants have stated that the "specification need not 'necessarily describe how to make and use every possible variant of a claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosure of embodiment, depending on the predictability in the art." However, the level of unpredictability for using pure toxin was high at the time Appellants filed the Application. **"**[I]t was believed at the time of filing the present application that pure botulinum toxin would not be effective for clinical use." Thus, one of ordinary skill could not "interpolate between embodiments, and perhaps even extrapolate beyond the disclosure of embodiment" to practice the claimed invention. Appellants simply have not provide any evidence that one could use only routine experimentation to practice the claimed invention even though ""**"**[I]t was believed at the time of filing the present application that pure botulinum toxin would not be effective for clinical use."

Appellants have argued that the conclusion of non-enablement has been premised on a single reference and does not take into account the evidence as a whole, including guidance and working examples in the parent application, prior art reference of Lamanna et al., and the declarations by Dr. Brin and Dr. Smith. However, all the evidence submitted by Appellants has been considered and taken into account in determining that the disclosure of the parent applications is non-enabling.

First with respect to guidance and working examples in the parent applications, Appellants state that the parent application "describes many examples of administration of a botulinum toxin." However, these examples in the specification utilize DYSPORT and BOTOX. BOTOX and DYSPORT are both commercially available toxin that are purified and contain the neurotoxic

component as a complex containing the Haemagglutinin. These complexes are simply not the same as the neurotoxic component as currently claimed. Looking to examples 2-2(e) in the parent applications, it is stated that the patient is injected with 100-1,000 units of Botulinum toxin type E, type B, type C, type D, type E and type F. However, the examples referenced do not use the word neurotoxic component. Appellants knew, at the time of filing, that the state of the art was that of Schantz. After all Appellants have said that Schantz was "reflective of the state of the art for when the present application was filed." Yet Appellants disclosure neither disclosed nor implied that pure toxin was clinically ineffective, as taught by Schantz. Further, Applicants did not provide any guidance to one of ordinary skill in the art how one could avoid the problems associated with purified botulinum toxin component. Specifically, the disclosure lacked any guidance as to how one of ordinary skill in the art could make the neurotoxic component less labile so it could be used in clinical settings. Rather, as Appellants stated, the disclosure simply gave a general teaching since the term Botulinum toxin is a generic term, implying that the knowledge of what was known for the complexed toxin could be used for non-complexed toxin. Even in the current Brief, Appellants state that botulinum toxin is "generic term used through out the specification to embrace the family of botulinum toxin, including the neurotoxic component." (see page 9 of Appellants Brief). However, as indicated by Schantz et al. the teachings of complexed toxin could not be utilized purified botulinum toxin since the purified potion is so labile that it would not be used in clinical settings.

With respect to the prior art references presented by Appellants and the Declaration, they do not sufficient present evidence to how one of ordinary skill in the art would make the pure toxin clinically viable. After all, as Appellants have stated "[A]t the time of the filing of the present application, one of ordinary skill would not consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings." As Appellants have stated, Lamanna et al

disclose formulation and storage of the botulinum toxin neurotoxic component. However, Lamanna et al. does not resolve the issue at hand. Namely how does one of ordinary skill in the art go about making the pure neurotoxin less labile so it could be used in clinical settings.?

Appellants also make reference to the Goodnough thesis and DasGupta. Appellants have stated these post filing references provide evidence of level of skill in the art at the time the application was filed. However, Appellant stance now is vastly different from those statements made in the response dated September 26, 2006. In that response, Appellants stated Schantz was more reflective of the state of the art when the present application was filed. While those statements may have been made in the context of obviousness and statements compared the state of the art relative to Tse, Appellants never the less concluded that Schantz was reflective of the state of the art. Appellant stated "**the disclosure of Schantz et al. is more current than Tse, and is more reflective of the state of the art for when the present application was filed**" and "it was believed at the time of filing the present application that pure botulinum toxin would not be effective for clinical use." Given these statements made by Appellants, Goodnough and DasGupta are not references that provide evidence of level of ordinary skilled in the art at the time the application was filed. The MPEP states that "[t]he state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." See MPEP 2164.05(a). The references and the Declarations simply do not provide evidence to the contrary prior to December of 1993 since the references relied upon were publicly available after the filing date of the instant application.

Assuming arguendo that the date was not in issue, the references do not provide any evidence to establish that the pure neurotoxin can be used in a clinical setting. Nothing in the reference establishes that the toxin was used in a clinical setting. The reference merely concludes

that the use of it as a pharmaceutical is "possible." All of the testing parameters were done on a "non clinical" setting which involved lethal doses to mice (see page 135 of Goodnough). The lyophilization experiments did not conclude the clinical viability of the lyophilized product. The Schantz reference stated that "No clinical trials on primates have been performed with purified neurotoxin" (see page 89 of Schantz) and "[b]ecause of its labiality the neurotoxin [pure] is not practical for medical applications." (see Page 82 of Schantz). The references simply do not establish that labiality is not an issue in the clinical setting.

With respect to the Declaration by Dr. Smith, while providing ample opinion evidence, it does not provide sufficient evidence to counter the conclusions of Schantz. The declaration states that the Schantz does not provide any evidence to support the conclusion. However, reviewing Schantz, the reference disclose, on page 82, pH, dilution at low concentrations, pH of greater than 7.3 the neurotoxin is liberated as the basis for its conclusions. Dr. Smith's declaration relies upon the reference of DasGupta as evidence that the statements made in Schantz are incorrect. However, this reference is post dated to Applicants invention. Remember that "The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." See MPEP 2164.05(a). Appellants have gone on record stating that Schantz is reflective of the state of the prior art when the Application was filed. Prior to Appellants' filing date, it was believed (and Appellants have asserted his on numerous occasions) purified botulinum toxin is so labile that it would not be used in clinical settings. The declaration simply does not provide evidence to the contrary prior to the filing date of December of 1993.

The Declaration by Dr. Brin, does not provide any evidence to counter the contentions raised by Schantz et al. While one of ordinary skill in the art may be able to make the neurotoxic component the Declaration does not set forth how one of ordinary skill in the art can use the toxic

component as claimed to treat the disorders as claimed "with little or no difficulty." The MPEP states "The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement." Here, the Declaration does not set forth any evidence, between the date of Schantz et al. and the filing date of the present invention, to rebut how at the time of the filing of the present application, one of ordinary skill would consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings, given the teachings of Schantz et al. The question was not whether one could make or isolate the purified toxin but whether one could use it in a clinical setting. The Brin declaration did not provide any evidence for this conclusion.

Finally Appellants argue that Schantz et al. was cited to establish a teaching away from the claimed invention. While Appellants may have cited the reference as a teaching away, their statements were not merely critical which would otherwise discourage the use of the pure toxin in the treatment stabismus. Rather, Appellants' statement raised question if one of ordinary skill in the art could use pure toxin at all. Again Appellants stated "it was believed at the time of filing the present application that pure botulinum toxin would not be effective for clinical use" and "Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. . ." In essence, Appellants' statements implied that the prior art was non-enabling with respect to using pure toxin in a clinical setting. A proper question of enablement was raised based on Appellants' statements made with respect to the state of the art. A proper review was conducted to see if the parent Application provided guidance on how one of ordinary skill in the art could make the pure toxin less labile so as to utilize it in a clinical setting. Reviews of the parent disclosure lead to the conclusion that it did not provide guidance. Thus, while the Appellants made the statement in the context of an obviousness rejection, it was

perfectly permissible to raise the question based on Appellants general belief that pure botulinum toxin is clinically ineffective.

Given the nature of the invention and the state of the art as recited by Schantz, guidance how one of ordinary skill in the art could make the neurotoxic component less labile so it could be used in clinical settings was **necessary and critical** to allow one of ordinary skill in the art to use pure toxin in a clinical setting. Without such guidance, one would be burdened with undue experimentation to practice the claimed invention. For these reasons, it is requested that the Board deny priority to Parent Applications 08/173,996 and 08/627,118.

Arguments Regarding obviousness under 35 USC §103

For both of the rejections under 35 USC §103, Appellants raise the same arguments. These arguments have been addressed below and are equally applicable to all of the rejections.

Appellants argue that they should be entitled to priority to December 23, 1993 and thus overcome the prior art rejection since Kohl and Aoki are published after 1993.

Assuming arguendo that the priority is not granted, Appellants argue "[t]here is no teaching or disclosure in the cited references, nor indeed any explicit rationale given by the Examiner, for why one of ordinary skill in the art would have modified the methods as disclosed in [the primary reference] in view of Tse, Kohl, Aoki and Han." Appellants state that primary references relate to injecting complexed toxin into a human spasmodic muscle for treating stabismus. However, Tse relates to injection of the neurotoxic component into a non-spasmodic rat hind leg muscle. Appellants make reference to Moyer et al. to conclude that information reported in the latter relating to the effects of the neurotoxic component on mouse muscles cannot be applied to human muscles.

Furthermore, Appellants argue that the teachings of Tse reference relate to improved vaccines and probes and not the treatment of stabismus. The goals of the to uses is entirely different.

Appellants argue that Kohl recites the use of 140kDa. "[T]he Examiner has not provided any evidence that the two neurotoxins are the same. As such, Applicants' position that the data regarding the use of the 140 kDa neurotoxic component in mice cannot be extrapolated to humans remains unchallenged."

Finally Appellants ague that the motivation to combine rely on the presumption that a physician would rely on the diffusion of the neurotoxic component to achieve a better treatment. However, highly diffusing toxins would diffuse to non-targeting muscles. "it appears that the Aoki reference is teaching away from the present invention, by teaching that the neurotoxic component would diffuse more quickly to adjacent muscles, and thus should not be used to treat stabismus. Indeed, it is the Applicant who surprisingly discovered that the neurotoxic component may be effectively used for treating stabismus. In view of the above, it is apparent that there is no rational basis for believing one of ordinary skill would have combined the cited references."

Response to Arguments

First, the priority issue has been addressed above and the priority should be denied. If priority is denied, the effective filing date is 5-21-03 (filing date of 10/443593) and Kohl, Aoki et al. and Han et al. are prior art to the claimed invention.

The MPEP states for a proper analysis of obviousness under 103 there must be "a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings [and] a finding that there was reasonable expectation of success." See

MPEP 2143. As Appellants have acknowledged, the rejection was based on "(1) the neurotoxic component has a similar activity in the paralysis of muscles as complexed neurotoxin; (2) the neurotoxic component has a similar activity against spontaneous release of acetylcholine; and (3) because botulinum toxin complexes (having a molecular weight greater than 150 kDa) may result in a slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection." Appellants' arguments fail to establish that the claimed invention is not obvious over the prior art or record.

Appellants argue different purposes of the references. However, Tse was cited to show that pure botulinum toxin specifically and characteristically inhibited stimulated and spontaneous release of acetylcholine at the vertebrate neuromuscular junction. The reference states that neurotoxin free of Haemagglutinin, when injected into the hind leg muscle of a rat, produced local paralysis within 24 hours (see page 494). Page 1-2 of Appellants' specification states, with regards to treating stabismus and other similar disorders, that "[t]he toxin [Botulinum toxin] binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in a local paralysis and hence relaxation of the muscle afflicted by spasm." Achieving paralysis is the mechanism by which the neuromuscular disorder such as stabismus is treated. Thus, the teaching relied upon in Tse are pertinent and in the same field as Applicants' invention, namely that the reference teaches the inhibition of acetylcholine release and the paralysis of muscles. The paralytic effect of the pure neurotoxin is also reflected in Kohl et al.

With respect to the rat studies and clinical efficiency of botulinum toxin, the reference of Kohl et al. addresses the concerns raised with respect to rat muscles. Kohl et al. teaches the administration of botulinum toxin NT-201, a highly purified botulinum toxin that consists of pure

neurotoxin. The results showed that that the paralytic effect of appears to be faster with NT-201 based on 20% CMAP decline. The maximum effect of this toxin was comparable to the complexed neurotoxin (see page 165). Note that the subjects used were human male volunteers. Note that this reference was cited in Hunt (US2003/0118598), which has the same Assignment as the instant application, as the basis to conclude that pure botulinum toxin can be formulated into pharmaceutical formulations for human use. "[P]ure botulinum toxin has been used in humans. see e.g. Kohl A., et al., Comparison of the effect of botulinum toxin A Botox (R)) with the highly-purified neurotoxin (NT201) in the extensor digitorum brevis muscle test, *Mov Disord* 2000;15(Suppl 3):165. Hence, a pharmaceutical composition can be prepared using a pure botulinum toxin." (see page 4, paragraph 043). Thus Kohl et al. establishes that the paralysis observed in rat muscles is also observed in human muscles. Accordingly, Kohl undermines Appellants' arguments that rat and human muscles are different and the effects of botulinum toxin cannot be extrapolated to one another. In fact Kohl provides a reasonable expectation of success to use pure toxin in human patients.

Appellants argue that Aoki et al. teaches away form the claimed invention. The point of Aoki's teaching is that, after administrate at the spot of treatment, the toxin diffused to the muscle to be treated more rapidly than complexed botulinum toxin. One would want the toxin to diffuse rapidly, away form the site of intramuscular injection, so as to treat and denervate the entire improperly functioning muscle. This would not only achieve better treatment of the disorder, but also rapid treatment of the disorder. Note that this assumption is reflected in Kohl et al. which states that the paralytic effect was faster with the pure neurotoxin in the muscle to be treated. This is the motivation of using the pure toxin in that it achieves a faster paralytic effect. Appellants have argued highly diffusing toxins would diffuse to non-targeting muscle. However, Appellants have not

presented any evidence that that rapid diffusion would result in diffusion to adjacent muscles, nor that faster paralytic effect would not be desired. Without evidence, Appellants arguments are merely speculative and do not establish a teaching away or lack of motivation.

Appellants have also argued that the 140 kDa neurotoxic component is not the same as the claimed "about 150 kilodaltons" neurotoxic component. First, it is not Kohl that teaches a molecular weight of about 140kDa. Rather it is Tse. Secondly, the propriety of the use of the expression "about" in claims to permit "of some tolerance" is established by long practice in the Patent Office. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 82 USPQ 303, 306 (Fed. Cir. 1983) and Ex Parte King, 82 USPQ 450, 451 (Pat. & Trademark Office Bd. App. 1948). The term "about" allows for some tolerance in the ranges disclosed. Thus, the term about implicitly discloses some variability even though the specification may not literally cite this variability.

Here, both the instant specification and the prior art use the word "about" in defining the molecular weight. Given the tolerance allowed by Courts, one can reasonably conclude that both the prior art toxin and the botulinum toxin disclosed in the instant application are the same. Furthermore, both the prior art and the instant application teach a toxin obtained form Clostridium botulinum and have the same activity in inhibition of acetylcholine release (see page 493 and 494 of Tse). Further, both toxins have a short polypeptide and long polypeptide. Given the source and the activity are the same in both the Appellants' disclosure and Tse et al. and both have a long and short polypeptide one can reasonably conclude that the pure botulinum toxin taught by Tse et al. is the same as the claimed invention. Furthermore, depending upon the methods utilized, such as SDS gel, one can attain different molecular estimates for the same compound. The MPEP states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of

either anticipation or obviousness has been established. When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." Here there is sound basis to conclude that the products are similar and thus, it is Appellants burden to show that they are not. Merely arguing difference in molecular weight is insufficient to establish that the products are different.

It is requested that the Board maintain the rejections under 35 USC §103.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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